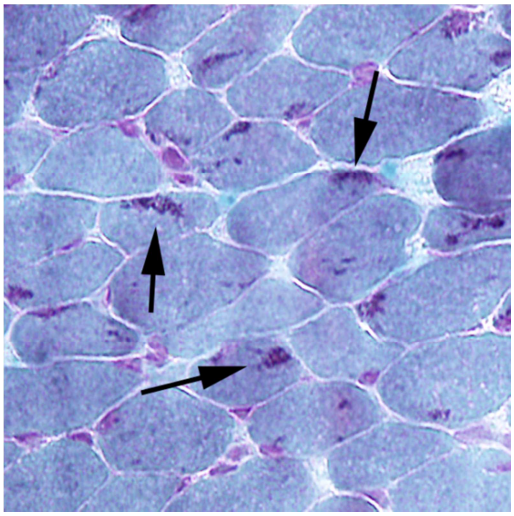
Nemaline myopathy

Nemaline myopathy is a genetic muscle condition that is classified as a congenital myopathy, which is an umbrella term for several conditions with distinctive changes on the muscle biopsy and relatively stable muscle weakness. Nemaline myopathy is diagnosed when large numbers of dense protein accumulations (called nemaline bodies or rods) are found in muscle cells under the microscopy and so this condition can only be diagnosed once a muscle biopsy has been performed. The severity of nemaline myopathy varies enormously between individuals. In the most severe form, some children with nemaline are so weak from birth that they are not able to breathe for themselves and even with intensive medical care, some children die in the first weeks or months of life. Most people with nemaline myopathy have mild or moderate muscle weakness in most muscles from birth, which often means they are slower than average to learn to walk and may struggle lifelong with stairs and with running. The swallowing muscles are often affected and some children take a long time to eat or may require tube feeds when they are young especially. If the muscles that control breathing (respiratory muscles) are weak, individuals may fall behind in their breathing, particular at night when sleeping. It pays to have regular breathing assessment to check for this. In young children the best test is a sleep study and lung function tests give useful information to doctors when children are old enough to manage this test. Reduced breathing overnight (nocturnal hypoventilation) is treated with a mask that supplies extra pressure to support breathing overnight (one form is called CPAP or continuous positive airways pressure) and this is usually very effective, even when the breathing muscles are quite weak. Even though the heart is a muscle, heart function is usually normal in people with nemaline myopathy. Children often improve in strength over the first few years of life, and strength may slowly decline from middle age but otherwise the degree of muscle weakness usually stays relatively stable in people with nemaline myopathy.



A muscle biopsy with nemaline myopathy. Note the nemaline rods, which appear as dark purple granules (arrows) inside muscle cells.

Nemaline myopathy is not a single condition, but it has many different possible genetic causes. So far we know of seven different genes that can be responsible but others likely remain undiscovered. Some of these forms of nemaline myopathy follow autosomal recessive inheritance patterns while for others, a dominant inheritance pattern is typical. Fact sheets about these patterns of inheritance are available on-line (http://www.genetics.edu.au/Information/Genetics-Fact-Sheets). Faults (mutations) in the code of any of these genes can lead to nemaline myopathy. Sometimes there are clues that a particular gene is responsible, but often it is difficult to predict the correct gene. As a result, it may take many years of testing various genes before doctors identify the gene responsible for nemaline myopathy in a particular family. Identifying the specific gene mutation is often helpful as it allows doctors to be more certain about the inheritance pattern that nemaline myopathy follows in that family and the chance that other family members might be affected, and it can allow doctors to individualise health care. Genetic testing in pregnancies, which is

sometimes considered when there is a risk of severe nemaline myopathy, is not possible until the specific gene mutation is identified in the family.

One of genetic causes of nemaline myopathy, the NEB gene that codes for a protein called nebulin, is so large that that it has been very difficult and expensive to test. Only recently has genetic testing for NEB been made available overseas and the high cost of testing has ruled this out for most situations, unless there are pressing reasons. This situation is about to change. Genetic testing is currently undergoing a revolution because of new techniques that have reduced the cost of testing multiple genes at once. It is likely that testing for all seven nemaline genes at once will become available in the near future, even for the enormous NEB gene. This is excellent news for nemaline myopathy families. The recent advances in genetic testing should also allow researchers to find all the currently unknown genes that cause nemaline myopathy over the next few years.

Over the last decade, doctors have become better at supporting children and adults with nemaline myopathy and keeping them well. Regular checks on breathing function, physiotherapy for optimising walking and joint position and surgery if a bend in the back develops (scoliosis) are all important. So far there is only evidence that one medication is helpful in nemaline myopathy, L-tyrosine, and the evidence for this medication is not strong. An international drug trial is currently being planned to gain more information about whether L-tyrosine is effective and which individuals with nemaline myopathy are likely to benefit. Research is ongoing to understand why muscles are weak in nemaline myopathy, in the hope that this will show researchers the best targets for treatments. Australian researchers are at the forefront of research on nemaline myopathy and are working to understanding this condition better to find effective treatments that improve muscle strength.

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